Is it Time for Immunotherapy Trials in Narcolepsy?

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COMMENTARY

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Commentary on Lecendreux et al. Intravenous immunoglobulin therapy in pediatric narcolepsy: a nonrandomized, open-label, controlled, longitudinal observational study. *J Clin Sleep Med*. 2017;13(3):441–453.

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Data from genetic, epidemiologic, and immunologic studies suggest an immune-mediated pathogenesis of narcolepsy type 1. The association with the HLA class II allele DQB1*06, which is much stronger than in many other known autoimmune diseases, and the description of triggering factors strongly support the concept of an autoimmune-mediated loss of hypocretin-producing cells.[1,2] Although results were conflicting, case series of few or single patients receiving different immune therapies, such as intravenous immunoglobulins, plasmapheresis, corticosteroids or the lymphocyte depleting monoclonal antibody alemtuzumab, challenged the question whether narcolepsy patients could benefit from such interventions.[3–9]

In the current issue of the *Journal of Clinical Sleep Medicine*, Lecendreux et al. report on the—thus far—largest longitudinal follow-up study of pediatric patients with narcolepsy treated with intravenous immunoglobulins (IVIg) as an off-label therapy in a large national reference center for narcolepsy. Overall, the results do not show a significant advantage of IVIg on narcolepsy symptoms in this cohort but the authors suggest a potential effect of the therapy in a subset of patients with more severe baseline symptoms.[10] Clearly the data have to be interpreted with caution and do not allow a definite conclusion on the efficacy of this immunotherapy in narcolepsy. Because the study is retrospective case series, lacking defined inclusion and exclusion criteria, there is an inherent bias in the selection of patients that is also reflected in the baseline characteristics of the study population. The authors have made all possible efforts to account for that bias in their statistical analysis, but were not able to fully delineate whether there was an independent effect of the IVIg treatment or whether it merely reflected a difference in the natural course of the disease. Nevertheless, there is a possibility that a subset of narcolepsy patients improved because of the treatment.

Such efforts are important to enhance our understanding of the disease but further steps are needed to advance the field toward new therapeutic approaches targeting specific immune processes in narcolepsy patients. Immunotherapeutic interventions provide an opportunity to approach essential questions on the immunopathogenesis of the disease. Therefore, controlled clinical trials should ideally be accompanied by thorough mechanistic studies aiming to dissect the main pathogenic components and identify biomarkers for future stratification of patients. Evidence for an autoantibody-mediated pathogenesis has been provided in different cohorts and distinct mechanisms have been described among patients with narcolepsy related to vaccination.[11–14] The role of the cellular immune response in the disease remains less clear and better understanding will guide targeted therapeutic strategies.[15,16]

An additional important aspect is to improve stratification of patients to increase the validity of future randomized clinical trials. Along with certain clinical aspects such as the association of narcolepsy with vaccination, research should focus on the development of appropriate biomarkers to identify patients who are more likely to respond to certain immune therapies.

Studies like the one by Lecendreux et al.[10] are essential to raise awareness about immune interventions in narcolepsy and help reduce the time gap between disease onset and treatment initiation. Although the study could not support the concept for early treatment, in some of the prior studies treatment effects were more promising if started early after disease onset.

Lecendreux et al. have made the first step toward therapeutic intervention studies in larger cohorts of pediatric patients with narcolepsy with a longer follow-up period. Finally, the time has come for randomized, controlled immunotherapy trials with the prospects for a new treatment era in narcolepsy.

CITATION

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